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Parietomotor connectivity in the contralesional hemisphere after stroke: A paired-pulse TMS study

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HIGHLIGHTS

- Anterior part of the intraparietal sulcus to primary motor cortex (M1) connectivity in the contralesional hemisphere was unaffected in stroke patients.
- Posterior part of the posterior parietal cortex (PPC) to M1 connectivity in the contralesional hemisphere was disrupted in stroke patients with spatial neglect.
- Disruption of posterior part of PPC to M1 connectivity correlated with the severity of peripersonal spatial neglect.

ABSTRACT

Objectives: To assess the contralesional connectivity between the posterior parietal cortex (PPC) and the motor cortex (M1) in stroke patients, and to probe putative relationships with spatial neglect and motor impairment.
Methods: In 12 right-side stroke patients and 12 age-matched healthy controls, we used paired-pulse transcranial magnetic stimulation to assess the contralesional connectivity between three left-side PPC sites (the anterior intraparietal sulcus (aIPS), the posterior intraparietal sulcus and the superior parieto-occipital cortex (SPOC)) and M1. The interstimulus interval (ISI) was set to 4 or 6 ms.
Results: Although there were no differences between the stroke patient group and the controls, a subgroup analysis showed that stimulation over the SPOC with an ISI of 6 ms facilitated motor-evoked potential responses in patients with neglect (and especially those with severe peripersonal neglect), relative to non-neglect patients. With an ISI of 4 ms, the aIPS exerted an inhibitory influence on M1 in all subjects. The severity of motor impairment was not associated with PPC-M1 connectivity.
Conclusions: aIPS-M1 connectivity seems to be unaffected in stroke patients, whereas connectivity from the most posterior parts of the parietal cortex depends on the patient's neglect status.
Significance: These results provide insight into post-stroke changes in contralesional PPC-M1 connectivity.

Abbreviations: PPC, posterior parietal cortex; PMC, premotor cortex; M1, motor cortex; aIPS, anterior part of the intraparietal sulcus; pIPS, posterior part of the intraparietal sulcus; SPOC, superior parieto-occipital cortex; TMS, transcranial magnetic stimulation; ppTMS, paired-pulse TMS; CS, conditioning stimulus; TS, test stimulus; ISI, interstimulus interval; FDI, first dorsal interosseous; MEP, motor evoked potential; RMT, resting motor threshold; N+, neglect patients; N−, non-neglect patients; FMA-UE, upper extremity subsection of the Fugl-Meyer Assessment; MAL-14, 14-item Motor Activity Log questionnaire.

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1. Introduction

Stroke is the main cause of acquired disability in adults. Upper limb paresis is one of the most frequent symptoms after stroke; the recovery of upper limb function is often problematic but constitutes a key factor in personal autonomy. Spatial neglect (defined as a failure to acknowledge or explore stimuli toward the contralesional side) (Heilman et al., 2000) is another challenging consequence of stroke, since it slows recovery and impairs activities of daily living (Di Monaco et al., 2011). In fact, spatial neglect is a frequent consequence of lesions in the right hemisphere – especially those affecting the inferior parietal, temporoparietal and superior parietal territories (Mort et al., 2003; Verdon et al., 2010; Molenberghs et al., 2012; Rousseaux et al., 2013). As a sensorymotor interface and a key structure in movement planning and control, the posterior parietal cortex (PPC) may play a role in post-stroke cerebral plasticity and recovery from both upper limb paresis and spatial neglect (Buneo and Andersen, 2006).

Parietofrontal networks (comprising the PPC, the premotor cortex (PMC) and the primary motor cortex (M1)) are significantly involved in the planning and online control of visually guided movements (Buneo and Andersen, 2006; Filimon, 2010; Davare et al., 2011; Vesia et al., 2013). More specifically, the most anterior structures of the PPC (i.e. the anterior part of the intraparietal sulcus (aIPS) and the supramarginal gyrus) are connected to the ventral PMC and control the grasping phase of movements (Davare et al., 2007; Koch et al., 2007, 2008a; Cavina-Pratesi et al., 2010; Koch et al., 2010; Vesia et al., 2013). In contrast, the most posterior structures in the PPC (i.e. the posterior part of the intraparietal sulcus (pIPS) and the adjacent cortical structures in the superior and inferior parietal lobule (the superior parieto-occipital cortex (SPOC) and the angular gyrus) are connected to the dorsal PMC and control the reaching phase (Makris et al., 2005; Koch et al., 2007, 2008a; Busan et al., 2009; Cavina-Pratesi et al., 2010; Karabanov et al., 2013; Vesia et al., 2013). Most of these findings on PPC-M1 functional connectivity come from paired-pulse transcranial magnetic stimulation (ppTMS) studies (for a review, see (Rothwell, 2011). At rest or just before movement initiation, a test stimulus (TS) is delivered to M1 a few milliseconds after a conditioning stimulus (CS) has been delivered to the PPC. Various studies of PPC-M1 connectivity in the left hemisphere have been performed in right-handed, healthy controls at rest. Depending on the intensity of CS and the length of the interstimulus interval (ISI, between the CS and the TS), one can variously observe an inhibitory influence of the CS when the latter is applied over the aIPS with an ISI of 4 ms (Koch et al., 2007; Karabanov et al., 2013; Vesia et al., 2013), a potentiating influence when the CS was applied over the pIPS (Koch et al., 2007; Karabanov et al., 2013), and the lack of an effect when the CS was applied over the SPOC (Vesia et al., 2013). However, SPOC-M1 connectivity may become functional during arm movements toward a target (Vesia et al., 2013).

Furthermore, transcallosal interparietal functional connections are asymmetric in right-handed healthy controls; the right PPC inhibits contralateral parietofrontal connections more strongly than the left PPC does (Koch et al., 2011). As a consequence, post-stroke neglect might result from the loss of interhemispheric balance between the right and left PPCs; this hypothesis is supported by the results of imaging studies in stroke patients (Rode et al., 2010; Bozzali et al., 2012; Lunven et al., 2015) and ppTMS studies in which contralesional (left) PPC-M1 connectivity was greater in right-handed patients with left spatial neglect than in patients without neglect or in healthy controls (Koch et al., 2008b, 2012). Subsequently, the application of repetitive TMS to the left PPC gave encouraging results in terms of recovery from peripersonal and behavioral neglect (for a review, see (Jacquin-Courtois, 2015). In these ppTMS studies, however, the CS was applied over the pIPS with a broad figure-of-eight coil; this probably activated posterior structures in the superior and inferior parietal lobules. Finally, a growing body of literature data suggests that parietofrontal networks are involved in post-stroke recovery from motor impairment (Inman et al., 2012; Schulz et al., 2015, 2016).

In summary, the PPC and the associated parietomotor networks are key structures not only for gesture planning and control but also for spatial representations. Parietofrontal networks seems to be involved in the genesis of spatial neglect and may be related to motor recovery – making the PPC a possible target for therapeutic modulation by non-invasive brain stimulation techniques. However, functional specialization has been evidenced for subregions of the PPC in humans, and little is known about this aspect in stroke patients. Indeed, to the best of our knowledge, contralesional connections between subregions of the PPC (the aIPS, pIPS and SPOC) and M1 have not previously been studied in stroke patients.

Hence, the primary objective of the present study was to compare left PPC-M1 connectivity in right hemispheric stroke patients and in healthy controls by using a ppTMS protocol to assess the effect of a CS (applied over the aIPS, pIPS and SPOC) on M1 excitability. The secondary objective was to assess the relationship between spatial neglect and motor impairment on one hand and left (contralesional) PPC-M1 connectivity on the other.

2. Methods

2.1. Study participants

Patients were recruited from among in- and outpatients in the Neurorehabilitation Unit at Lille University Medical Center (Lille, France) between August 2014 and February 2016. We included 12 stroke patients who had suffered a single right ischemic or hemorrhagic hemispheric stroke (diagnosed by MRI) and had displayed left hemiparesis for at least 6 months before inclusion. The presence of spatial neglect was not an inclusion criterion but was assessed in all included patients (see 2.5). We also included 12 healthy age-matched healthy controls. We excluded patients with bilateral lesions, those who were unable to consent to or understand the study protocol due to language, cognitive or psychiatric disorders, and those presenting contraindications to TMS or MRI. All participants were right-handed, according to the Edinburgh Handedness Inventory (Oldfield, 1971), and gave their informed written consent to participation. The study was approved by the local investigational review board (*Comité de protection des personnes Nord Ouest IV*, Lille, France; reference 2013-A01766-39), and was conducted in accordance with the tenets of the Declaration of Helsinki.

2.2. Experimental procedures

The participants were seated in a comfortable chair, with their right forearm resting on a second chair (the height of which could be adjusted). They were told to keep their arm still throughout the experimental session. As the first dorsal interosseous (FDI) muscle is activated during both phases of prehension movements (Koch et al., 2008a; Davare et al., 2009), motor evoked potentials (MEPs) were recorded at this site. Electromyographic (EMG) activity was recorded with Ag–AgCl surface electrodes in a belly-tendon montage. The electrodes were positioned over the body of the muscle and the first metacarpophalangeal joint. A ground electrode was attached to the wrist. The EMG signals were amplified (×1000), high-pass filtered at 10 Hz, low-pass filtered at 1000 Hz (Digitimer,